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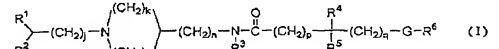
(54) **CYCLOAMINE CCR5 RECEPTOR ANTAGONISTS**

(57) Remedies or prophylactics for diseases in association with CCR5 such as AIDS, rheumatoid arthritis or nephritis comprising a cyclic amine compound represented by the following formula (I), a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C_1-C_6 alkyl addition salt thereof, as an active ingredient.



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Description

Technical Field

[0001] The present invention relates to CCR5 antagonists expectable of effects as remedies and/or prophylactics for diseases in which infiltration and activation of monocytes/macrophages, T-cells and the like into tissues play an important role in progression and maintenance of the diseases such as rheumatoid arthritis, nephritis (nephropathy), multiple sclerosis, rejection after organ transplantation, graft-versus-host diseases (GVHD), diabetes, chronic obstructive pulmonary diseases (COPD), asthma, atopic dermatitis, sarcoidosis, fibrosis, atherosclerosis, psoriasis and inflammatory bowel diseases or AIDS (acquired immunodeficiency syndrome) caused by infection of HIV (human immunodeficiency virus).

Background Art

[0002] The CCR5 is a receptor for MIP-1α (an abbreviation for macrophage inflammatory protein-1α), MIP-1β (an abbreviation for macrophage inflammatory protein-1β) or RANTES (an abbreviation for regulated upon activation normal T-cell expressed and secreted) and is known to be expressed in lymphoid tissues such as thymus and spleen, monocytes/macrophages, T-cells or the like (see, for example, Samson, M. et al., Boichemistry, 1996, 35, 3362; Raport, C.J. et al., J. Biol. Chem., 1996, 271, 17161; and Combadiere, C. et al., J. Leukoc. Biol., 1996, 60, 147).

[0003] As to information about the relationship between the CCR5 and diseases, it has been reported that the CCR5 was expressed in leukocytes such as T-cells in arthrosynovial tissues and synovial fluid of patients suffering from rheumatoid arthritis (see Loetscher, P. et al., Nature, 1998, 391, 344; Mack, M. et al., Arthritis Rheum., 1999, 42, 981 and the like), CCR5 deficient homozygotes were not found in patients suffering from rheumatoid arthritis (see Gomez-Reino, J.J. et al., Arthritis Rheum., 1999, 42, 989), CCR5 was expressed in T-cells in renal biopsy samples of patients suffering from glomerulonephritis, interstitial nephritis and rejection after transplantation (see Segerer, S. et al., Kidney Int., 1999, 56, 52), many T-cells expressing CCR5 were found in blood of patients suffering from multiple sclerosis (see Balashov, K.E., Proc. Natl. Acad. Sci. USA, 1999, 96, 6873), CCR5 was expressed in T-cells infiltrated into liver injury sites of a mouse graft-versus-host disease (GVHD) model and the infiltration of the T-cells was suppressed by administration of an anti-CCR5 antibody (see Murai, M. et al., J. Clin. Invest., 1999, 104, 49), the progression of morbid states in a mouse diabetes model was associated with MIP-1α and CCR5 (see Cameron, M.J. et al., J. Immunol., 2000, 165, 1102) and the like.

[0004] Accordingly, CCR5 is thought to be associated with initiation, progression and maintenance of diseases in which the accumulation and activation of monocytes/macrophages and/or T-cells in disease sites can be assumed to be deeply associated with progression of lesions, for example rheumatoid arthritis, nephritis (nephropathy), multiple sclerosis, rejection after organ transplantation, graft-versus-host diseases (GVHD) and diabetes.

[0005] Furthermore, based on a report that the CCR5 is specifically expressed in Th1 cells among the T-cells, CCR5 is thought to be associated with initiation, progression and maintenance of many autoimmune diseases and inflammatory diseases such as chronic obstructive pulmonary diseases (COPD), asthma, atopic dermatitis, sarcoidosis, fibrosis, atherosclerosis, psoriasis and inflammatory bowl diseases in which Th1 cells can be assumed to be associated with morbid states including the above diseases (see Bonecchi, R. et al., J. Exp. Med., 1998, 187, 129; Loetscher, P. et al., Nature, 1998, 391, 344 and the like).

[0006] On the other hand, although CD4 is known as a receptor when a host cell is infected with HIV (human immunodeficiency virus), it has been suggested that a second receptor (a coreceptor receptor) is necessary because the infection of HIV is not established only with the CD4. Usually, HIV-1 is roughly classified into a macrophage-tropic (M-tropic) strain and a T-cell-tropic (T-trophic) strain depending on the species of cells that the virus can infect, and it has been elucidated that a coreceptor essential to the infection of the macrophage-tropic strain is CCR5 (see, for example, Deng, H. et al., Nature, 1996, 381, 661; Dragic, T. et al., Nature, 1996, 381, 667; Alkhatib, G. et al., Science, 1996, 272, 1955; Choe, H. et al., Cell, 1996, 85, 1135; and Doranz, B.J. et al., Cell, 1996, 85, 1149).

[0007] Therefore, drugs capable of inhibiting the binding of HIV-1 to CCR5 are thought to be effective as new remedies and/or prophylactics for AIDS (acquired immunodeficiency syndrome) (see Michael, N.L. et al., Nature Med., 1999, 5, 740; Proudfoot, A.E.I. et al., Biochem. Pharmacol., 1999, 57, 451; Murakami et al., Protein, Nucleic Acid and Enzyme, 1998, 43, 677 and the like). As information supporting the above inference, it has been reported that RANTES, MIP-1α and MIP-1β which are ligands of CCR5 were suppressive factors for HIV-1 infection (see Cocchi, F. et al., Science, 1995, 270, 1811), humans without expressing normal CCR5 at all by deficiency of 32 base pairs of CCR5 gene had resistance to HIV-1 infection and any other abnormality in health is not caused by the deficiency (see Liu, R. et al., Cell, 1996, 86, 367; Samson, M. et al., Nature, 1996, 382, 722; Dean, M. et al., Science, 1996, 273, 1856 and the like), anti-CCR5 monoclonal antibodies inhibited the infection of peripheral blood monocytes by macrophage-tropic HIV-1 (see Wu, L. et al., J. Exp. Med., 1997, 185, 1681), RANTES in which the amino terminals were missing or modified

was an antagonist of the RANTES to inhibit the infection with macrophage-tropic HIV-1 (see Arenzana-Seisdedos, F. et al., Nature, 1996, 383, 400; Proost, P. et al., J. Biol. Chem., 1998, 273, 7222; Simmons, G. et al., Science, 1997, 276, 276 and the like) and the like.

[0008] As mentioned above, a compound which inhibits the binding of MIP-1α, MIP-1β or RANTES that is an in vivo ligand of the CCR5 to the CCR5 or the binding of HIV-1 which is a pathogenic virus of AIDS to the CCR5, i.e. a CCR5 antagonist is thought to be useful as a remedy and/or prophylactic for diseases such as AIDS, rheumatoid arthritis, nephritis (nephropathy), multiple sclerosis, rejection after organ transplantation, graft-versus-host diseases (GVHD), diabetes, chronic obstructive pulmonary diseases (COPD), asthma, atopic dermatitis, sarcoidosis, fibrosis, atherosclerosis, psoriasis or inflammatory bowel diseases.

[0009] It has recently been reported that substituted bis-acridine derivatives (see WO9830218), substituted anilide derivatives (see WO9901127; WO0006085; WO0006146; WO0006153; WO0040239;and WO0042852), substituted alkenanilide derivatives (see WO9932100; WO0010965; WO0037455; and Baba, et al., Proc. Natl. Acad. Sci. USA, 1999, 96, 5698), 3-(4-piperidinyl)Indole derivatives (see W09917773 and W0042045), azacycloalkane derivatives (see EP1013276; WO0038680; and WO0039125) benzodipyran derivatives (see WO0053175) and pyrrolidine derivatives (see WO0059497; WO0059498; WO0059502; and WO0059503) have an antagonistic activity against CCR5. These compounds, however, are different from the compounds used in the present invention.

[0010] On the other hand, although the compounds used in the present invention are the same as those described in WO9925886, the compounds are not known to have the antagonistic activity against the CCR5.

Disclosure of the Invention

[0011] It is an object of the present invention to provide a small-molecular compound having the inhibitory activity against the binding to the CCR5, i.e. a CCR5 antagonist.

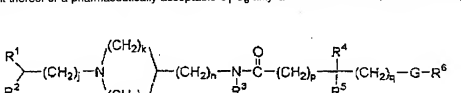
[0012] It is another object of the present invention to provide a small-molecular compound having the inhibitory activity against the binding of an in vivo ligand of the CCR5 such as RANTES to CCR5 on target cells or the inhibitory activity against the binding of HIV-1, which is a pathogenic virus of AIDS to the CCR5.

[0013] It is a further object of the present invention to provide a remedial and/or prophylactic method for diseases in which the binding of an in vivo ligand of CCR5 to CCR5 on target cells is one of pathogeneses.

[0014] It is still another object of the present invention to provide a remedial method and/or a prophylactic method for AIDS caused by HIV infection.

[0015] As a result of intensive studies, the inventors have found that cyclic amine derivatives having an arylalkyl group, pharmaceutically acceptable C_1-C_6 alkyl addition salts thereof or pharmaceutically acceptable acid addition salts thereof have the CCR5 antagonistic activity. Furthermore, studies have been promoted according to findings that those compounds can be useful as remedies or prophylactics for diseases considered to be in association with CCR5. Thereby, the present invention has been accomplished.

[0016] Namely, according to the present invention, there are provided a medicine having the CCR5 antagonistic activity and comprising a compound represented by the following formula (I), a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C_1-C_6 alkyl addition salt thereof, as an active ingredient:



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wherein, R^1 is a phenyl group, a C_3-C_8 cycloalkyl group or an aromatic heterocyclic group having one to three oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group or the aromatic heterocyclic group in the above R^1 may be condensed with a benzene ring, or an aromatic heterocyclic group having one to three oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C_3-C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R^1 may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, C_2-C_6 alkenyl groups, C_1-C_6 alkoxy groups, C_1-C_6 alkylthio groups, C_3-C_5 alkylene groups, C_2-C_4 alkylenoxy groups, C_1-C_3 alkylenedioxy groups, phenyl groups, phenoxy groups, phenylthio groups, benzyl groups, benzyloxy groups, benzoylamino groups, C_2-C_7 alkanoyl groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoyloxy groups, C_2-C_7 alkanoylamino groups, C_2-C_7 N-alkylcarbamoyl groups, C_4-C_9 N-cycloalkylcarbamoyl groups, C_1-C_6 alkylsulfonyl groups, C_3-C_8 (alkoxycarbonyl)methyl groups, N-phenylcarbamoyl groups, piperidinocar-

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